AN OVERVIEW OF CLINICAL AND PHYSIOPATHOLOGICAL FEATURES OF THROMBOTIC THROMBOCYTOPENIC PURPURA DURING PREGNANCY

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP), haemolytic-uraemic syndrome (HUS), preeclampsia-HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, and some other autoimmune syndromes like catastrophic antiphospholipid syndrome (CAPS), are microangiopathic disorders that can be diagnosed during pregnancy. Although the underlying physiopathological mechanisms differ, the clinical consequences are very similar in all of them, so that it is very difficult to establish a differential diagnosis. Since each disease has its own treatment particularities, and maternal and perinatal morbidity and mortality are high when treatment is not appropriate, gynaecologists need to have a thorough understanding of differentiating characteristics of these disorders. TTP is more common in women, with a peak incidence in the fourth decade of life, and 10% of all cases occur during pregnancy. In the absence of adequate diagnosis and treatment, the maternal and foetal mortality rate approaches 90%. Preconceptional counselling should be provided to women with prior episodes of TTP or congenial Upshaw-Schulman syndrome.

Keywords: Thrombotic thrombocytopenic purpura, high-risk pregnancy, plasma exchange, plasmapheresis, perinatal mortality, maternal mortality.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is one of the microangiopathic disorders that can be diagnosed during pregnancy. These alterations are characterised by the formation of microthrombi in small vessels, leading to thrombocytopenia, microangiopathic haemolytic anaemia, and multiple organ damage. The hypercoagulability state observed during pregnancy conditions the incidence of such disorders in pregnant women compared with the general population. Specifically, these disorders comprise TTP, haemolytic-uraemic syndrome (HUS), preeclampsia-HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, and some other autoimmune diseases like catastrophic antiphospholipid syndrome (CAPS).

TTP is clinically characterised by a group of five symptoms: thrombocytopenia, microangiopathic haemolytic anaemia, fever, neurological alterations, and renal failure. It can exhibit a familial trait, though idiopathic TTP is the most common presentation. HUS in turn is characterised by renal failure, and although it is typically observed in children with a history of infection due to toxin-producing bacteria in the previous days or weeks, the disease occasionally has also been reported during pregnancy. On the other hand, both preeclampsia and HELLP syndrome belong to a range of disorders in which arterial hypertension is the fundamental clinical feature - HELLP syndrome being one of the most serious conditions. On the other hand, CAPS is a serious and rapidly progressive form of antiphospholipid syndrome leading to multiple
organ failure. CAPS may be the first manifestation of the disease, although previous history of antiphospholipid syndrome, systemic lupus erythematosus, or in a small number of cases, Sjögren's syndrome or systemic sclerosis, could guide the doctor. In CAPS, the activation of coagulation is caused by the presence of autoantibodies that bind to membrane phospholipids. Although the underlying physiopathological mechanisms differ, the clinical consequences are very similar. This makes it very difficult to establish a differential diagnosis. Each disease has its own treatment particularities, and maternal and perinatal morbidity and mortality are high when treatment is not appropriate. It is therefore necessary for gynaecologists to have a thorough understanding of differentiating characteristics of these disorders.

Epidemiology and Presentations

The reported incidence of TTP in the general population is 3.8 cases per million individuals. In turn, the incidence of TTP and HUS, as disorders differentiated on the basis of laboratory test criteria, is one case in every 25,000 pregnancies and one case in every 198,000 pregnancies, respectively. TTP is more common in women, with a peak incidence in the fourth decade of life, and 10% of all cases occur during pregnancy. The incidence of TTP shows a female/male ratio of 3:2, possibly because of the greater female susceptibility towards autoimmune disorders. Pregnancy triggers both the appearance of the disease and its recurrence. TTP associated to pregnancy accounts for 10-30% of all cases of TTP diagnosed in adults.

TTP can manifest in three clinical forms. One form is familial-hereditary congenital disease or Upshaw Schülman syndrome (SUS), which accounts for a mere 5% of all cases in the general population and 24% of all cases associated with pregnancy, while a second form is acquired idiopathic disease (the most frequent presentation), and a third form is related to use of drugs, infections, neoplasms, and pregnancy. The disease often evolves in the form of outbreaks. In this sense, following remission of the initial episode, recurrences of the clinical symptoms are typically observed, particularly during the first year after the diagnosis.

The inclusion, in some series of pregnant women with minor forms of TTP or with probable HELLP syndrome, results in reported maternal mortality rates of <10%. However, in the absence of adequate diagnosis and treatment, the maternal and foetal mortality rate approaches 90%. In this context, unlike in HELLP syndrome or severe preeclampsia, there is no evidence that uterine evacuation is able to solve the problem; a correct differential diagnosis is therefore of crucial importance. TTP as either an initial episode or recurrence can manifest at any time during pregnancy, though the condition is more often diagnosed in advanced gestation, during the second or third trimester, in peripartum, or even in the puerperal period.

TTP was first described in 1924 by Eli Moschcowitz in a 16-year-old girl who developed haemolytic anaemia, thrombocytopenia, neurological alterations, and impaired renal function, followed by death due to cerebral infarction and heart failure. The autopsy revealed generalised thrombosis, particularly of the terminal arterioles. The first documented case of TTP during pregnancy was reported in 1955, in a 30-year-old woman in the eighth month of pregnancy, who died as a result of the disease.

Physiopathology

Von Willebrand factor (vWF) is a multimeric glycoprotein fundamentally produced in the endothelial cells, where it accumulates in the Weibel-Palade bodies, and in megakaryocytes, conforming the so-called alpha granules. These intracellular vWF multimers are larger (ultra-large multimers) than those that circulate freely in plasma under normal conditions (large multimers). The ultra-large multimers are able to bind with greater affinity than the large multimers to the platelet glycoprotein Ib (GPIb) receptors, thereby favouring platelet aggregation. Regulation of multimer size is therefore essential in order to maintain adequate function. vWF also has zones for binding to the vascular endothelium and platelets, favouring their adhesion to activated platelets, facilitating their aggregation, and to factor VIII, preventing the latter from undergoing premature degradation. Regulation of multimer size is mediated by a metalloproteinase known as ADAMTS-13 (A disintegrin and metalloproteinase with a
thrombospondin type 1 motif, member 13) that cleaves the ultra-large multimers as they are secreted, converting them into chains that are anchored in the collagen of the vascular wall or circulate freely.18

Defects in degradation of the ultra-large vWF multimers give rise to the different forms of TTP. The existence of ultra-large vWF multimers in the plasma of patients with recurrent TTP was reported in 1982. These multimers would increase platelet adherence to the endothelium, particularly in high-flow vessels (capillaries), thereby favouring the appearance of thrombi.19,20

In the familial forms of the disease (SUS), homozygous mutation of the gene encoding for the synthesis of ADAMTS-13 (chromosome 9) causes the protease activity to drop to <5% of that seen under normal conditions.21 The familial form usually begins to manifest during childhood, though in some cases it develops later in life, and occasionally during pregnancy. Many mutations have been identified in relation to ADAMTS-13 deficiency, with variable impact in relation to the clinical severity of the condition. Approximately 90% of all patients with both homo and heterozygous mutations present symptomatic TTP.22,23 In the acquired forms, protease activity is either low or absent during the disease outbreaks, and recovers during the disease-free intervals. In these cases the existence of an anti-ADAMTS-13 IgG autoantibody has been identified. The production of autoantibodies may be transient and/or recurrent, thereby conditioning the course of acquired idiopathic TTP. Autoantibodies can be detected in approximately 31-38% of all patients with idiopathic TTP.

Increased circulating oestrogen levels have been related to an increase in coagulation factors such as factor VIII and vWF, as well as to a decrease in the protease activity of the enzyme ADAMTS-13.25 This circumstance is another factor giving rise to an increased incidence of TTP among women and its occurrence or relapse during pregnancy,26 and is co-responsible for the hypercoagulability state seen during pregnancy.27,28 A significant observation is the fact that 100% of all patients with SUS who do not receive prophylactic treatment initially develop the disease or experience recurrences during pregnancy, and an important percentage suffer their first episode upon becoming pregnant. On the other hand, 25% of all patients with acquired TTP develop recurrences during pregnancy or in the immediate puerperal period.

Despite knowledge of the mentioned physiopathological aspects of the disease, doubts remain regarding the existence of still unknown additional aetiopathogenic factors. The fact that there have been reports of cases of acquired idiopathic TTP in which the ADAMTS-13 levels are normal, or of familial TTP characterised by a complete absence of ADAMTS-13 without clinical manifestations until adult age, points to the need for further investigation of the pathogenesis of this disease.29 Quantification of ADAMTS-13 in the disease-free intervals contributes to distinguish among the different forms of the disease. In this sense, values of <10% of normal are typical of hereditary TTP, while values >30% are indicative of acquired TTP.3

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

Between 10-40% of the patients experience pseudo-influenza syndrome in the weeks prior to diagnosis, and asthaenia, malaise, and fever for days or weeks, refractory to initial empirical symptomatic treatment, are occasionally observed. The classical group of five clinical symptoms is observed in 40% of the cases, while 75% of all patients exhibit a triad in the form of microangiopathic haemolytic anaemia, thrombocytopenia, and neurological symptoms such as headache, diminished consciousness, or seizures.30 It is also possible to observe moderate renal dysfunction, with creatinine levels <3 mg/dL, though both neurological and renal disorders are more common in the terminal stages of untreated cases. It must be also taken into account that cardiac abnormalities may be important and are often unrecognised causes of mortality and morbidity in patients with TTP.31 Cardiac symptoms are frequently overlooked because many patients are young, without cardiac risk factors, but angina, congestive heart failure, arrhythmias, and syncope have been reported in >20% of TTP patients and myocardial infarctions appear in 24% of autopsies. In the absence of clear evidence for cardiac involvement, all TTP patients should be screened with a focused cardiac history, electrocardiogram and serial cardiac enzymes, and should be monitored.31,32
Because of the need for early diagnosis and adequate treatment, the five clinical characteristics regarded as crucial for diagnosing the disease have been reduced to only two: thrombocytopenia and microangiopathic haemolytic anaemia. Thus, in daily practice, the presence of thrombocytopenia (<20x10^9/L), schistocytes representing >1% of the global red cell population, and lactate dehydrogenase (LDH) elevation in the absence of other apparent causes, suffice to diagnose TTP and start treatment. Since in this way TTP is indistinguishable from HUS, some authors include both conditions under the term TTP-HUS. The role of the determination of ADAMTS-13 and ultra-large vWF multimers in characterising the different microangiopathic disorders is unclear. ADAMTS-13 activity varies between 50-78% in healthy adults, though during pregnancy the variability is usually lower, and only in cases of SUS are activity values of <5% observed. There have been reports of patients who develop an episode of TTP with ADAMTS-13 levels >50%. In turn, some patients with activity levels <5% remain disease-free, and some series have reported higher mortality in cases of TTP during pregnancy than in idiopathic PTT in non-pregnant patients, independently of the ADAMTS-13 activity level.

It should be mentioned that HELLP syndrome occurs in 0.5-0.9% of all pregnancies and affects 10-20% of all patients with severe preeclampsia. Both TTP and preeclampsia HELLP syndrome occur more frequently in the second half of pregnancy, in the peripartum or postpartum. Establishing a differential diagnosis is therefore complicated since the clinical manifestations are very similar. However, while the end of pregnancy contributes to treatment in cases of preeclampsia HELLP syndrome, the clinical course of TTP or HUS is not modified. The need for an adequate differential diagnosis has caused the diagnosis of TTP-HUS to be considered in those pregnant women who, beyond week 24, present microangiopathic haemolytic anaemia (negative indirect Coombs’ test) and thrombocytopenia in the absence of arterial hypertension and/or proteinuria, as well as in pregnant women in the first or second trimester (<24 weeks) in which any of the orienting symptoms are suspected, in view of the low frequency of HELLP syndrome in these gestational weeks. The shorter the interval from symptoms onset to the start of treatment, the better the perinatal outcomes.

Regarding CAPS, diagnostic criteria include: 1) evidence of involvement of three or more organs, systems and/or tissues; 2) development of events simultaneously or in less than a week; 3) pathologic confirmation of occlusion of small vessels in at least one organ or tissue, and 4) laboratory confirmation of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies).

### Table 1. Clinical and laboratory findings.

<table>
<thead>
<tr>
<th></th>
<th>TTP</th>
<th>HUS</th>
<th>HELLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)</td>
<td>20-75</td>
<td>80-90</td>
<td>85</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>With haematuria</td>
<td>80-90</td>
<td>90-95</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>20-50</td>
<td>Not reported</td>
<td>Absent</td>
</tr>
<tr>
<td>Nausea and vomiting (%)</td>
<td>Common</td>
<td>Common</td>
<td>40</td>
</tr>
<tr>
<td>Abdominal pain (%)</td>
<td>Common</td>
<td>Common</td>
<td>60-80</td>
</tr>
<tr>
<td>Central nervous system (%)</td>
<td>60-70</td>
<td>Not reported</td>
<td>40-60</td>
</tr>
<tr>
<td>ADAMTS13 activity 5%</td>
<td>33-100</td>
<td>Rare</td>
<td>Absent</td>
</tr>
<tr>
<td>von Willebrand factor multimers (%)</td>
<td>80-90</td>
<td>90</td>
<td>Absent</td>
</tr>
<tr>
<td>Platelet count (mm^3)</td>
<td>&gt;20,000</td>
<td>&lt;20,000</td>
<td>&lt;20,000</td>
</tr>
<tr>
<td>Anaemia (%)</td>
<td>100</td>
<td>100</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Elevated transaminases (%)</td>
<td>Usually absent</td>
<td>Usually absent</td>
<td>100</td>
</tr>
<tr>
<td>Elevated lactic dehydrogenase (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Adapted from Stella CL et al.
On the other hand, the effects of hepatic insufficiency due to acute fatty liver of pregnancy should be considered in TTP differential diagnosis. This disorder has uncertain aetiology but inherited defects in the mitochondrial beta-oxidation of long chain fatty acids are associated. Clinical manifestations include abdominal pain, headache, nausea, vomiting, anorexia, and jaundice. The 20% is associated with preeclampsia, and very often coagulopathy secondary to severe hepatic impairment appears. Transaminases are often >300-500 IU/L. Typical laboratory findings in acute fatty liver of pregnancy include bilirubin >2 mg/dL, hypocholesterolaemia <200 mg/dL, hypoglycaemia <60 mg/dL, hypofibrinogenaemia <300 mg/dL, decreased antithrombin III, and prothrombin time prolongation.

TREATMENT

The initial treatment of TTP-HUS during pregnancy is no different from that indicated in the non-pregnant patient. Patients with SUS benefit from prophylactic treatment with fresh plasma infusions every 2-3 weeks, according to the ADAMTS-13 activity levels. TTP is potentially fatal, with a mortality rate of >90% before introduction of the current treatments. The prognosis, in terms of maternal-foetal survival rates, has improved since the 1970s with the development of treatments such as plasma transfusions and plasmapheresis. The mortality rate has dropped to approximately 10-20%, with a response in up to 90% of all cases of TTP, and healing rates of up to 80%. Plasmapheresis is the most effective treatment option and should be started as soon as possible. Even when the diagnosis is uncertain, the possible complications of TTP outweigh the risks of such treatment. Plasma administration while plasmapheresis is started may be useful. In fact, when plasma exchange cannot be started immediately, it is advisable to start the infusion of high fresh plasma doses under constant central venous pressure control in order to avoid volume overload. Pregnancy does not appear to modify treatment response, though the effects upon the foetus have not been evaluated.

Plasmapheresis is able to eliminate circulating anti-ADAMTS-13 autoantibodies and ultra-large vWF multimers from plasma. The infusion of fresh plasma in turn helps restore the deficient ADAMTS-13 levels. A schematic representation of treatment for acute TTP episodes is provided.
Figure 1. Schematic representation of treatment for acute TTP episodes.
PEX; plasma exchange; CVC: central venous catheter.
Adapted from George JN.⁵⁷

in Figure 1. Corticosteroids have some effect in the treatment of TTP episodes. Before the generalised use of plasma exchange therapy, some authors reported a favourable response in 55% of the patients with neurological disorders when using high-dose corticosteroids.⁵³ Subsequent studies have shown the benefit of high-dose corticosteroids as adjuvant therapy (dexamethasone 10 mg/kg/day for 3 days and 2.5 mg/kg/day thereafter).⁵⁴

Although antiplatelet treatment could seem adequate from the physiopathological perspective, some studies have found it to increase bleeding risk. The administration of antiplatelet drugs is therefore not generalised.⁵² Nevertheless, some recent clinical guides suggest the administration of 75 mg/day of acetylsalicylic acid if the platelet count is >50x10⁹/L.⁵⁵ The risk of venous thromboembolism has never been formally quantified in acute TTP but is likely to be increased due to immobility and acute illness. Therefore routine low molecular weight heparin (LMWH) thromboprophylaxis should be given once the platelet count has recovered to >50x10⁹/L.⁵⁵,⁵⁶ Platelet transfusion should be reserved for patients with life-threatening bleeding problems, since the worsened clinical condition reported by different authors after platelet transfusion suggests that it worsens microangiopathic disorder.⁴⁷ If platelet transfusion proves necessary, it should always be associated to plasma replacement therapy.⁵²,⁵⁷

In patients refractory to treatment (10-20% of all cases), and when exacerbations of the acute episode occur in under 30 days after normalisation of the platelet count, a monoclonal antibody (rituximab) has been shown to be effective as second-line treatment.⁵⁸ An 88% success rate has been reported with the administration of rituximab in refractory cases.⁵⁹ This monoclonal antibody allows faster recovery of the platelet count, lowers the circulating autoantibody titres, and increases ADAMTS-13 activity.⁶⁰ Rituximab is able to normalise the platelet count within an average of 2 weeks, with remission of the condition in 5 weeks, and is
effective in preventing relapse during the year following treatment. The use of rituximab during pregnancy has been associated with neonatal neutropenia, though it has been administered in the first 3 months of pregnancy without neonatal adverse effects.\textsuperscript{61} Although some studies have reported benefits with other drugs, randomised studies are needed to clarify the role of agents such as vincristine, cyclophosphamide, or immunoglobulins via the intravenous route in the treatment of TTP in pregnancy.

**PROGNOSIS**

Before the introduction of plasma exchange, maternal survival in cases of TTP related to pregnancy was very limited, with a mortality rate of >90%. However, following the introduction of this treatment modality, the maternal mortality rate has dropped to 0-10%. At present, morbidity remains high, with neurological damage in up to 10% of all cases and renal damage in 21%.\textsuperscript{61,62} In some series the perinatal mortality rate reaches\textsuperscript{3,63} 80%, and is usually related to hypoxia due to placental vascular lesions secondary to thrombotic occlusion of the decidual arterioles. No cases of idiopathic TTP to newborn infants have been reported.

Since treatment with plasmapheresis must be started urgently after the onset of symptoms, any delay in establishing the diagnosis has negative consequences. An adequate differential diagnosis must be established between TTP and HELLP syndrome, since the treatment in each case differs, and confusing the two diseases has been associated with increased maternal mortality.\textsuperscript{64,65} The ending of pregnancy does not improve the course of TTP. It therefore should only be performed when there is evidence of foetal distress or growth retardation, concurrent preeclampsia, or in cases where plasma exchange proves ineffective. Perimortem caesarean delivery has been described in patients with TTP following irreversible cardiorespiratory arrest.\textsuperscript{66}

The risk of relapse in subsequent pregnancies in the case of hereditary TTP is 100% in the absence of plasma-based preventive treatment. The latter therefore must be started as soon as possible in the first trimester.\textsuperscript{67} The risk of relapse in a subsequent pregnancy in women with acquired idiopathic TTP associated to severe ADAMTS-13 deficiency is relatively low (close to 20%).\textsuperscript{69} Therefore, with appropriate prenatal management and correct planning, future pregnancy in patients with antecedents of TTP is reasonably safe.

The general recommendation for controlling pregnancies of this kind is to closely monitor the patients during pregnancy and start prophylactic plasmapheresis every 2 weeks if the ADAMTS-13 activity falls to under 10% or blood smears yield unequivocal evidence of red cell fragmentation (schistocytes), suggesting the presence of haemolytic anaemia.\textsuperscript{41} Plasmapheresis is recommended before delivery. The management of patients with TTP during pregnancy should be established on an individualised basis. As a general rule it is accepted that if a patient with a prior diagnosis of TTP becomes pregnant, a first test of ADAMTS-13 activity is useful. In this way plasma exchange can be indicated if necessary, with adoption of the necessary controls.

On the other hand, pregnant or puerperal women who develop severe thrombocytopenia (<50x10\(^9\)/L) as a component of HELLP syndrome may benefit from rapid ADAMTS-13 activity testing to determine whether urgent plasma exchange could offer benefit instead of other methods, since none of the published series have found HELLP to be associated with severe ADAMTS-13 deficiency. The LDH/glutamic-oxaloacetic transaminase (GOT) ratio is very high in cases of TTP, since the LDH levels are far higher than in HELLP syndrome, while GOT is only slightly elevated. On the other hand, if a patient diagnosed with HELLP syndrome is unable to reach platelet counts >25x10\(^9\)/L after 8-12 hours of treatment with dexamethasone 10 mg, it is prudent to assume a diagnosis of TTP.\textsuperscript{13}

According to the recent clinical guides (Grade IA recommendation), mothers with congenital TTP should visit a specialised centre to receive ADAMTS-13 through the infusion of fresh plasma on a regular basis throughout pregnancy and during puerperium if necessary.\textsuperscript{55} Close coordination between haematologists and obstetricians with an interest in maternal-fetal medicine is required in patients with TTP (Grade IA recommendation). Counselling before conception is very important, providing information about the risks posed by pregnancy as a relapse-triggering factor (Grade IIB recommendation).\textsuperscript{55}
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